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Dexmedetomidine to Reduce Vasopressor Resistance in Refractory Septic Shock: α2 Agonist Dexmedetomidine for REfractory Septic Shock (ADRESS): A Double-Blind Randomized Controlled Pilot Trial

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OBJECTIVES: Increasing evidence has suggested the benefits of dexmedetomidine in patients with sepsis. Dexmedetomidine may increase vasopressor sensitivity, which may be of interest in the setting of refractory septic shock. The α2 Agonist Dexmedetomidine for REfractory Septic Shock (ADRESS) pilot study aimed to evaluate the effect of dexmedetomidine on the vasopressor response in patients with refractory septic shock.

DESIGN: This study was a multicenter, randomized, placebo-controlled, double-blind pilot trial.

SETTING: The study was conducted in 5 ICUs in France.

PATIENTS: Inclusion criteria were septic shock (Sepsis-3 definition) and norepinephrine requirement greater than or equal to 0.25 μg/kg/min (0.5 μg/kg/min of norepinephrine tartrate) with persistent circulatory failure (defined by lactate > 2 mmol/L, oliguria, or skin mottling) and invasive mechanical ventilation.

INTERVENTIONS: The arterial pressure response to phenylephrine was measured before starting the treatment (0 hr), at 6 hours (primary outcome), and 12 hours. In the treatment arm, dexmedetomidine was given at a fixed dose of 1 μg/kg/hr.

MEASUREMENTS AND MAIN RESULTS: Inclusions were stopped early because of higher mortality in the dexmedetomidine arm. Thirty-two patients of the 36 planned were included. Response to phenylephrine at 6 hours was lower in the dexmedetomidine group than in the placebo group (1.26 ± 0.23 vs. 1.45 ± 0.26; $p = 0.048$), although this difference was also observed at baseline ($p = 0.029$). There were no significant differences between the groups in terms of cumulative norepinephrine dose, lactatemia, Sequential Organ Failure Assessment score, fluid balance, ventilation-free days, or occurrence of bradycardia. Mortality on day 3 was higher in the dexmedetomidine group than in the placebo group, with a difference that diminished and was no longer significant on 30 and 90 days.

CONCLUSIONS: Patients in the dexmedetomidine arm had a significantly lower response to phenylephrine at all study times including baseline, which might have contributed to higher early mortality in the dexmedetomidine arm and preclude to conclude on dexmedetomidine efficacy in refractory septic shock. However, heart rate was not decreased in the dexmedetomidine arm.

KEYWORDS: alpha-2 agonists; dexmedetomidine; refractory septic shock; septic shock; vasopressors

Early deaths (≤ 3 d) during septic shock account for 30–50% of fatalities (1, 2) and are primarily due to persistent circulatory failure, known as refractory septic shock (RSS). RSS is mainly characterized by persistent

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KEY POINTS

Question: Does dexmedetomidine allow to decrease vasopressor resistance in patients with refractory septic shock?

Findings: In this pilot randomized controlled trial, sensitivity to phenylephrine was not increased 6 hours after dexmedetomidine initiation. At all study times (baseline, 6, and 12 hr), patients in the dexmedetomidine arm had a significantly lower response to phenylephrine.

Meaning: The results of this study does not allow to draw conclusions on dexmedetomidine efficacy to alleviate vasopressor resistance in refractory septic shock patients.

arterial hypotension and increased catecholamine doses (3, 4), although there is no universal definition (3,5,6). Vasoplegia is strongly linked to mortality in septic shock (7) and is often caused by blood vessel resistance to vasoactive hormones like catecholamines (8), as shown by altered dose-response curves to phenylephrine (9, 10). Septic shock also involves significant sympathetic hyperactivation with high levels of circulating endogenous catecholamines (11, 12).

Experimental studies with alpha-2 agonists as sympatholytics have shown promising results, including improved survival, inflammatory response, and blood pressure (13–15). A subgroup analysis from the trial of Pandharipande et al (16), comparing lorazepam to dexmedetomidine, indicated a survival benefit and reduced vasopressor requirements with alpha-2 agonists (17). This was confirmed by a post hoc analysis of septic shock patients from the Sedation Practice in Intensive Care Evaluation (SPICE III) trial (18), showing reduced vasopressor requirements with dexmedetomidine (19). Similar effects were noted in cardiac surgery contexts (20). These results may appear counter-intuitive due to the typically hypotensive side effects of alpha-2 agonists.

The hypothesis is that sepsis-induced adrenoreceptor down-regulation is a consequence of sympathetic hyperactivation, and alpha-2 agonists could restore vasopressor responsiveness by normalizing this activation (21). Experimental studies found that clonidine and dexmedetomidine restored norepinephrine response to baseline in lipopolysaccharide-challenged rats (22), confirmed in ovine sepsis models (23, 24).

A recent randomized controlled trial showed dexmedetomidine-reduced mortality in severe sepsis and septic shock patients (25, 26), with smaller trials showing similar benefits and reductions in cytokine levels and capillary leak index (27–30). Meta-analyses reported dexmedetomidine's beneficial effects on mortality, Sequential Organ Failure Assessment (SOFA) score, and mechanical ventilation duration in sepsis and septic shock patients (31, 32).

Overall, data suggest alpha-2 agonists' use for sympathetic deactivation may be particularly beneficial in cases of profound vasopressor hyporesponsiveness, as seen in RSS.

As a first step before a large controlled trial, we decided to conduct an exploratory, pilot study for several reasons: 1) to confirm the safety of this drug in this particular context, as intensivists may be reluctant to use dexmedetomidine in the context of shock, due to the usual effects of this drug such as hypotension and bradycardia; 2) to assess the feasibility and recruitment potential; and 3) to possibly confirm the vasopressor-enhancement effect of the drug in this specific population of patients, which would justify its use.

Thus, this pilot trial aimed to evaluate the direct effect of dexmedetomidine on vasopressor response in patients with RSS and assess the effect size and safety to support the feasibility and help to design a larger trial with mortality as a primary outcome.

METHODS

Trial Design and Population

The detailed study protocol has been previously published (33) and is available in the **Supplementary Material** (http://links.lww.com/CCM/H698). The α2 Agonist Dexmedetomidine for REfractory Septic Shock (ADRESS) pilot study was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial, conducted in four ICUs in France.

Eligibility criteria were: 1) admission diagnosis of septic shock (Sepsis-3 criteria [34]); 2) refractory shock defined as a) norepinephrine base equivalent greater than or equal to 0.25 μg/kg/min (0.5 μg/kg/min of norepinephrine tartrate) reached within 24 hours after ICU admission, b) persistent circulatory failure with one or more of the following present within 2 hours of

randomization: arterial lactate greater than 2 mmol/L; mottling score greater than or equal to 1 (35); oliguria (< 0.5 mL/kg/hr); and 3) requiring mechanical ventilation and sedation with either propofol or midazolam. Main exclusion criteria were (full list is available in the protocol): 1) cardiac arrest before inclusion; 2) cardiac index less than 2.2 L/min/m^2 OR left ventricular ejection fraction less than 40%; and 3) decision to withhold life-supporting therapy. Hemodynamic monitoring was protocolized (Supplementary Material, http://links.lww.com/CCM/H698) with repeated measurement of cardiac output, preload dependency evaluation using echocardiography and/or transpulmonary thermodilution.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Central Ethics Committee (Ethics Committee Sud-Est VI, Clermont-Ferrand, France, May 2019, European Union Drug Regulating Authorities Clinical Trials n°2019-000726-22, ClinicalTrials.gov NCT03953677) and by the National Drug Agency (Agence Nationale du Médicament [ANSM]) in April 2019. All patients and/or their next/of kin gave informed and signed consent. When the patient was unable to give consent before inclusion, consent was signed by a proxy person and the informed consent of the patient was systematically sought whenever it was possible.

Study Interventions

Phenylephrine Challenge. We used a validated continuous perfusion protocol (9, 10) (Supplementary Material, http://links.lww.com/CCM/H698). Briefly, phenylephrine was infused continuously in successive 5 minutes dose increments at 1, 2, 3, and 6 µg/kg/min. At each dose level, mean arterial pressure (MAP) and heart rate (HR) were averaged.

Immediately after enrollment, a first phenylephrine challenge was performed to determine baseline vasopressor responsiveness by measuring the dose-response relationship with MAP (9, 10). Zero hour defined the time of the first phenylephrine challenge completion and was repeated 6 hours ± 30 minutes (6 hr) and 12 hours ± 30 minutes (12 hr) after the end of the initial phenylephrine challenge.

Randomization and Blinding. The study participants were randomly assigned in a 1:1 ratio. Following randomization, the hospital pharmacy provided randomized treatment in blinded, sealed boxes. The treatment was prepared by a nurse who was hailed from a distinct care unit.

Study Treatment. Patients randomized to the dexmedetomidine arm received dexmedetomidine (DEXDOR, 100 µg/mL; OrionPharma, Espoo, Finland) at a fixed dose of 1 µg/kg/hr (0.7 µg/kg/hr for the first 2 hr). The placebo arm received continuous infusion of 5% glucose. Study treatment was initiated immediately after completion of the first phenylephrine challenge. Criteria for discontinuation were norepinephrine requirement less than or equal to 0.1 µg/kg/min and/or discontinuation of sedation. Prescription of target Richmond Agitation-Sedation Scale (RASS) score and reevaluation of sedative doses were planned.

Primary Outcomes

The primary outcome was the MAP response to phenylephrine at 6 hours (6 hr after the completion of the first phenylephrine challenge), expressed as a percentage (baseline MAP compared with MAP obtained with the maximum phenylephrine dose [$\%MAP_{dmax}$]).

Secondary Outcomes

The secondary endpoints were as follows:

Efficacy Outcomes. The efficacy outcomes were as follows: 1) course of response to phenylephrine between 0, 6, and 12 hours; 2) cumulative and peak dose of norepinephrine at 6 and 12 hours; 3) blood pressure during the first 24 hours, with percentage of time spent within the 65 mm Hg MAP target; 4) lactate at randomization 6 and 12 hours; 5) SOFA score from day 0 to day 3; 6) cumulative fluid balance and resuscitation fluid volume, over the first 3 days; 7) number of days without mechanical ventilation over the first 28 days; 8) number of days without vasopressors over the first 28 days; 9) mortality at day 3, during ICU stay, and at 90 days; and 10) mottling score at 6 hours and 12 hours.

Safety Outcomes. Occurrence of severe bradycardia (HR < 50 beats/min [bpm], requiring intervention) during the treatment duration.

Feasibility Outcomes. Recruitment potential based on the screening logs in each center, feasibility of randomization, and blinding procedures.

Data Collection

Data extraction softwares (iCollect; General Electric Healthcare, Chicago, IL; and RECAN; Alpha-2, Lyon, France) were used to extract the data directly from the monitors. In the first 24 hours, electrocardiogram and invasive blood pressure were continuously extracted and saved to allow blinded analysis of phenylephrine challenge and other cardiovascular outcomes. Data were analyzed offline and blinded to the randomization arm. Norepinephrine doses were recorded hourly after the ICU admission.

Safety

Adverse events were collected during the trial. Events of special interest included: bradycardia less than or equal to bpm requiring intervention, death from refractory shock, and severe hypoglycemia. An independent data and safety monitoring board (DSMB) reviewed unblinded study data for safety.

Statistical Analysis

The mean blood pressure response to phenylephrine in RSS patients was 122% ± 25% (10). Assuming a 25% improvement with dexmedetomidine, a 5% alpha risk, and 80% power, the estimated sample size was 16 patients per group. To accommodate nonanalyzable patients, the target sample size was set at 36 patients. Statistical analyses were conducted using SAS, Version 9.4 (SAS Institute, Cary, NC), with significance defined as a two-tailed p value of less than 0.05. Categorical variables are shown as numbers and percentages, and continuous variables as mean ± SD or median (interquartile range), based on distribution. Group characteristics were compared using the chi-square or Fisher exact test, or the Student t test or Mann-Whitney U test, as appropriate. Analyses were conducted on an intention-to-treat basis, with a planned per-protocol analysis excluding major protocol deviations. The treatment arm's effect on MAP response to phenylephrine over time (from 0 to 12 hr) was analyzed using an analysis of variance model on repeated measurements, testing arm, time, and interaction effects. The maximum drug Effect (Emax) model with random effects analyzed the full dose-response curves (9, 36), comparing the two treatment groups according to the Emax and Effective Dose 50 (ED50) parameters (detailed methods in Supplementary Material, http://links.lww.com/CCM/H698).

RESULTS

Population Characteristics

The flowchart of the study is presented in **Figure 1**. Thirty-two patients were enrolled between October 2019 and January 2023 (enrollment was suspended during 12 mo during the COVID-19 pandemic). After the second planned meeting, the independent DSMB observed a higher mortality rate at day 3 in the dexmedetomidine arm and recommended the end of the trial after randomization of 32 patients. Patient characteristics are presented in **Table 1**. The response to phenylephrine was significantly decreased at baseline in patients randomized to the dexmedetomidine arm (1.27 ± 0.2 vs. 1.44 ± 0.2; $p = 0.0291$).

Study Treatment Characteristics

The median time from randomization to start of study treatment was 2.30 hours (1.70–2.63 hr). The median duration of the study treatment was 1 day in the dexmedetomidine arm and 2 days in the placebo arm.

Response to Phenylephrine Challenge

MAP response to phenylephrine at 6 hours was higher in the placebo compared with the dexmedetomidine arm (1.45 ± 0.26 vs. 1.26 ± 0.23; $p = 0.048$). Results of sensitivity analyses were slightly different after: 1) exclusion of patients with Simplified Acute Physiology Score II greater than 100 ($n = 2$, dexmedetomidine arm): 1.45 ± 0.26 vs. 1.27 ± 0.25 in the placebo and dexmedetomidine arm, respectively; $p = 0.074$ and 2) exclusion of patients with a baseline $\%MAP_{dmax}$ phenylephrine response below the 90th percentile ($n = 2$, dexmedetomidine arm): 1.45 ± 0.26 vs. 1.30 ± 0.22 in the placebo and dexmedetomidine arm, respectively; $p = 0.128$. At 12 hours, MAP response was also higher in the placebo arm (1.50 ± 0.26 vs. 1.28 ± 0.23; $p = 0.031$).

The evolution of MAP response to phenylephrine (from 0 to 12 hr) is shown in **Figure 2**. The interaction

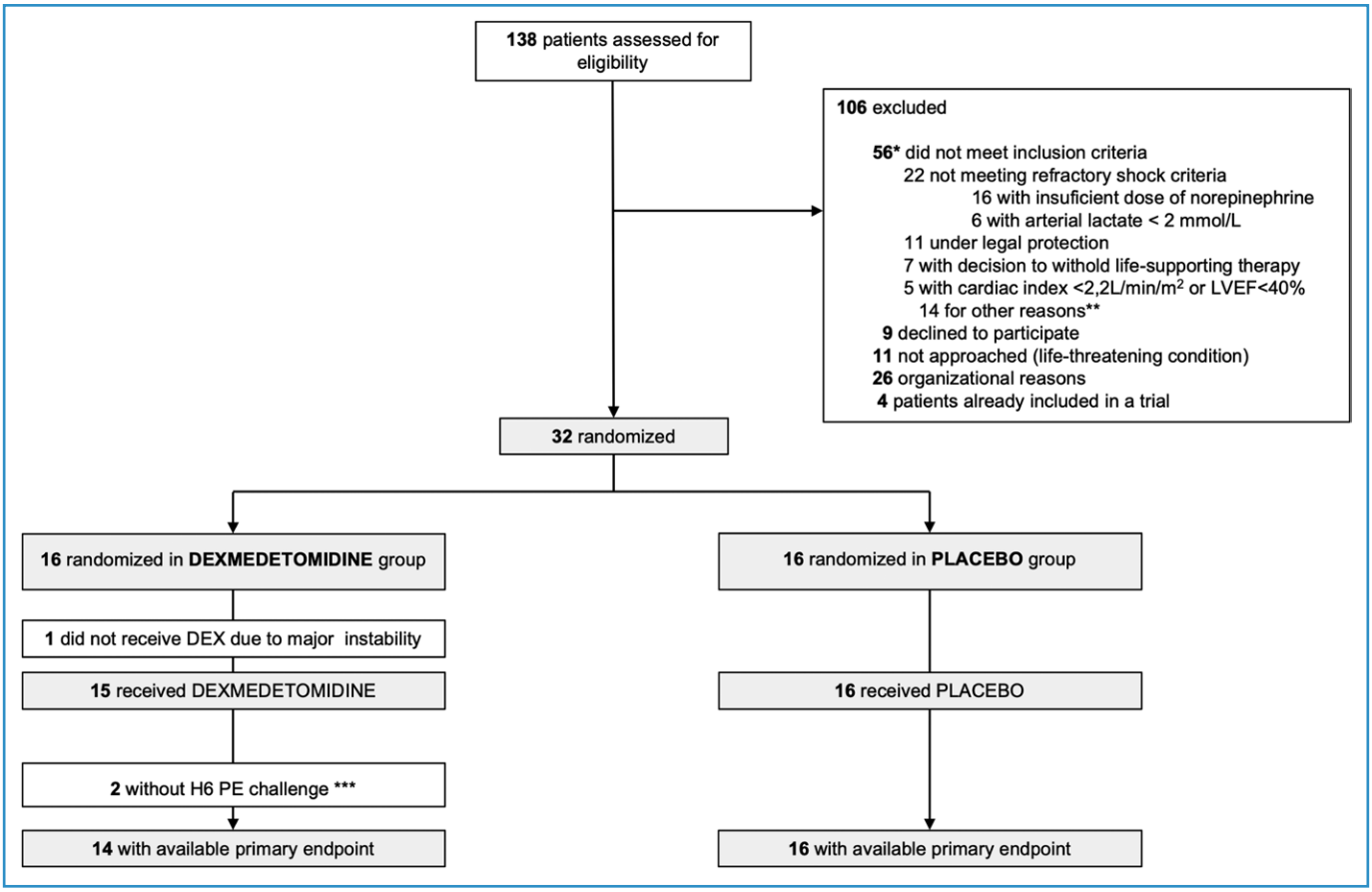
138 patients assessed for eligibility
106 excluded
56* did not meet inclusion criteria
22 not meeting refractory shock criteria
16 with insuficient dose of norepinephrine
6 with arterial lactate < 2 mmol/L
11 under legal protection
7 with decision to withold life-supporting therapy
5 with cardiac index <2,2L/min/m2 or LVEF<40%
14 for other reasons**
9 declined to participate
11 not approached (life-threatening condition)
26 organizational reasons
4 patients already included in a trial
32 randomized
16 randomized in DEXMEDETOMIDINE group
16 randomized in PLACEBO group
1 did not receive DEX due to major instability
15 received DEXMEDETOMIDINE
16 received PLACEBO
2 without H6 PE challenge ***
14 with available primary endpoint
16 with available primary endpoint

Figure 1. Flow chart of the α2 Agonist Dexmedetomidine for REfractory Septic Shock (ADRESS) pilot study. *Three patients met several noninclusion criteria. **Other reasons include severe acute liver failure ($n = 4$), mesenteric ischemia ($n = 3$), norepinephrine greater than 24 hr ($n = 3$), acute cerebrovascular disease ($n = 2$), with sedation without propofol or midazolam ($n = 1$), and cardiac arrest before inclusion ($n = 1$). ***No phenylephrine (PE) challenge due to early death. DEX = dexmedetomidine, LVEF = left ventricular ejection fraction.

between time and arm was not significant ($p = 0.90$). The response evolution (time effect) was not significant ($p = 0.45$).

The Emax response threshold was not significantly different between the two arms ($p = 0.4$ at 0 hr; $p = 0.88$ at 6 hr and $p = 0.63$ at 12 hr; **Supplementary Table 1** and **Supplementary Fig. 1**, http://links.lww.com/CCM/H698). The ED50 parameter showed a higher MAP growth speed in the placebo arm ($p = 0.016$ at 0 hr, $p = 0.024$ at 6 hr, and $p = 0.053$ at 12 hr).

Circulatory Parameters and Norepinephrine Requirements

Continuously monitored hemodynamic parameters were averaged in 1-hour windows (**Fig. 3**). The MAP course was similar between the groups (Fig. 3*A*), with nonsignificant differences at every time point. At the time of treatment start, patients in the dexmedetomidine arm received a nonsignificantly higher norepinephrine dose (1.00 ± 0.6 vs. 0.66 ± 0.50 µg/kg/min; $p = 0.11$; Fig. 3*B*). The MAP/norepinephrine ratio analysis showed similar results (Fig. 3*C*). Peak norepinephrine dose was higher at 6 hours or death in the dexmedetomidine arm (1.84 ± 1.07 vs. 0.96 ± 0.61 µg/kg/min; $p = 0.01$), but cumulated norepinephrine dose was not significantly different between arms (**Table 2**). The norepinephrine course in individual patients in the dexmedetomidine and placebo arms is shown in **Figure 4**. The percentage of time spent above the MAP target was not significantly different between the dexmedetomidine and placebo arms (79% ± 28% vs. 88% ± 19%, respectively; $p = 0.406$). There was no significant difference in HR during monitoring between the treatment arms (Fig. 3*D*). Lactatemia, mottling score, cardiac index, and ventilator-free days did not significantly differ between arms (Table 2). Fluids and fluid balance data are presented in **Supplementary Table 2** (http://links.lww.com/CCM/H698).

TABLE 1.
Baseline Patients Characteristics

Variables	Dexmedetomidine ($n = 16$)	Placebo ($n = 16$)	p
Sex, male	11 (69%)	11 (69%)	1
Age, yr	62.2 (± 16.1)	67.1 (± 11.2)	0.32
Body mass index, kg/m^2	27.0 (± 5.9)	28.4 (± 9.4)	0.61
Charlson's score (37)	2.1 (± 2.2)	2.4 (± 2.4)	0.76
Major comorbidities			
Myocardial infarction	2 (13%)	0	0.14
Congestive heart failure	4 (25%)	0	0.03
Peripheral vascular disease	1 (6%)	3 (19%)	0.28
Cerebrovascular disease	0	4 (25%)	0.03
Chronic pulmonary disease	0	2 (13%)	0.14
Cirrhosis	2 (13%)	1 (6%)	0.27
Diabetes	6 (38%)	6 (38%)	0.30
Chronic kidney disease (moderate/severe)	2 (13%)	4 (25%)	1
Simplified Acute Physiology Score II	75.3 (± 15.9)	66.4 (± 13.3)	0.09
Sequential Organ Failure Assessment score	12.9 (± 2.7)	11.8 (± 2.6)	0.26
Sepsis origin			
Pulmonary	5 (31%)	8 (50%)	0.28
Urinary	3 (19%)	2 (13%)	1
Peritonitis	3 (19%)	3 (19%)	1
Catheter-related	2 (13%)	0	1
Other[a]	3 (19%)	3 (19%)	1
Positive bacterial culture	8 (50%)	10 (67%)	0.48
Midazolam	8 (50%)	8 (50%)	1
Propofol	8 (50%)	8 (50%)	1
Sufentanyl	11 (69%)	14 (88%)	0.39
Norepinephrine dosage (μg/kg/min)	0.8 (± 0.6)	0.7 (± 0.5)	0.45
MAP (mm Hg)	68.5 (± 10.4)	73.8 (± 7.2)	0.10
MAP/norepinephrine ratio (mm Hg/μg/kg/min)	238 (± 160)	428 (± 424)	0.11
Lactate (mmol/L)	8.1 (± 5.9)	6.0 (± 4.2)	0.25
Mottling score	1.6 (± 1.7)	1.5 (± 1.4)	0.82
Cardiac index (L/min/m^2)	3.38 (± 1.24)	3.06 (± 1.04)	0.44
Baseline (0 hr) phenylephrine challenge			
Norepinephrine (μg/kg/min)	0.9 (± 0.5)	0.7 (± 0.5)	0.25
MAP (mm Hg)	72.7 (± 10.8)	74.9 (± 9.0)	0.54
MAP/norepinephrine ratio (mm Hg/μg/kg/min)	248 (± 168)	356 (± 284)	0.22
MAP response (final MAP/baseline MAP)[b]	1.27 (± 0.2)	1.44 (± 0.2)	0.029

MAP = mean arterial pressure.

[a]Other infections included: meningitis, endocarditis, cervical cellulitis, and angiocholitis.

[b]$p = 0.0291$ and unknown ($n = 2$).

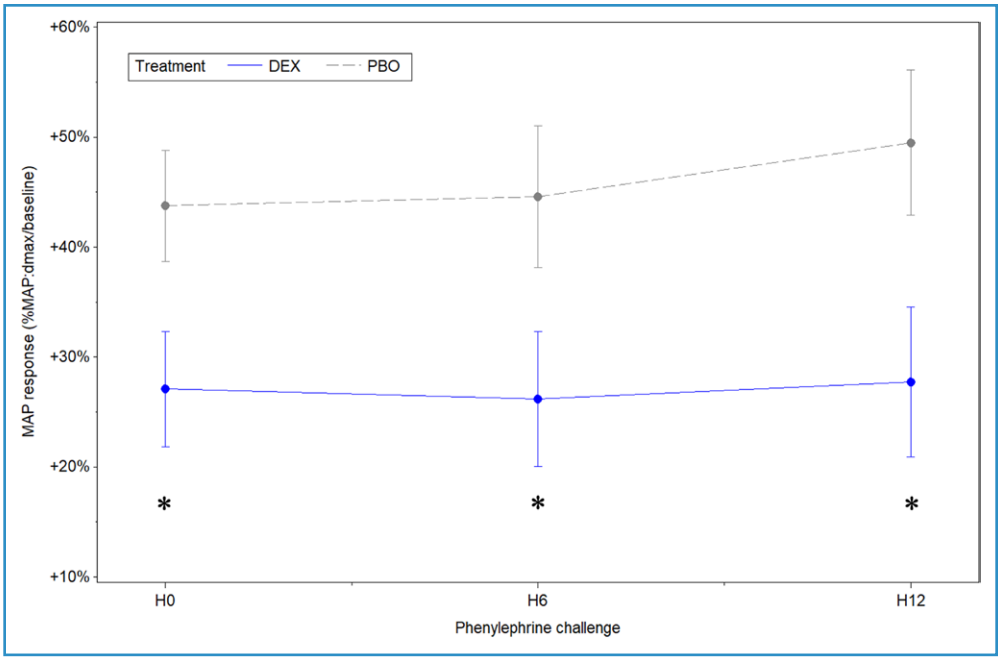

Figure 2. Response to phenylephrine (PE) challenge (baseline mean arterial pressure [MAP] compared with MAP obtained with the maximum PE dose [% MAP_{dmax}]) evolution from 0 to 12 hr. Means and corresponding variances are represented. *Asterisks* indicate $p < 0.05$. DEX = dexmedetomidine, PBO = placebo.

Sedation

Sedative doses were not decreased in the dexmedetomidine arm. Mean dose of midazolam and propofol were higher in dexmedetomidine patients in the first day (13 ± 6 vs. 9 ± 4 mg/hr; $p = 0.10$ and 179 ± 59 vs. 131 ± 88 mg/hr; $p = 0.22$), as well as in the next 3 days (nonsignificant; Table 2). There was no difference in RASS scores in the first 3 days.

Safety Outcomes

The average HR during monitoring was similar (108 ± 26 vs. 105 ± 27 bpm in dexmedetomidine and placebo; $p = 0.795$), as was the minimal HR during monitoring (68 ± 26 vs. 71 ± 19 bpm in dexmedetomidine and placebo; $p = 0.436$). Episodes of severe bradycardia requiring intervention was reported in one patient (in the dexmedetomidine arm). The patient experienced multiple organ failure with continuous venovenous hemodialysis and persistent acidosis with severe hyperkalemia (widened QRS intervals). Bradycardia and hyperkalemia persisted after the treatment was stopped, and the patient died the following day with multiple organ failure and refractory shock.

Mortality

The early mortality rate was significantly higher in the dexmedetomidine arm, with 8 (50%) and 2 (13%) deaths occurring by day 3 ($p = 0.022$). Mortality remained higher at subsequent time points: 11 (69%) vs. 6 (40%) deaths on day 30 ($p = 0.108$), 10 (63%) vs. 6 (38%) deaths during the ICU stay ($p = 0.157$), and 11 (69%) vs. 9 (60%) deaths on day 90 ($p = 0.611$).

Per Protocol Analysis

Four patients with major protocol deviations were excluded from the dexmedetomidine arm: one did not meet inclusion criteria, two had life-supporting therapy withdrawn in the first 24 hours, and one received no study treatment due to refractory shock. The results, detailed in **Supplementary Table 3** (http://links.lww.com/CCM/H698), favored the placebo arm for the primary outcome (1.45 ± 0.26 vs. 1.24 ± 0.19; $p = 0.0259$). The difference in early mortality between dexmedetomidine and placebo (42% vs. 13%; $p = 0.078$), as well as cumulative vasopressor doses and ventilator-free days, was no longer significant.

Feasibility

To facilitate recruitment, the norepinephrine threshold was adjusted from 1 to 0.25 µg/kg/min within the first 24 hours, along with the criterion of persistent circulatory failure. Initially, only one patient was enrolled in 6 months, but after this adjustment and a pandemic-related interruption, the remaining patients were enrolled steadily over 24 months, with a maximum of three centers open simultaneously.

DISCUSSION

In this pilot randomized trial in patients with RSS, sensitivity to phenylephrine was lower in patients

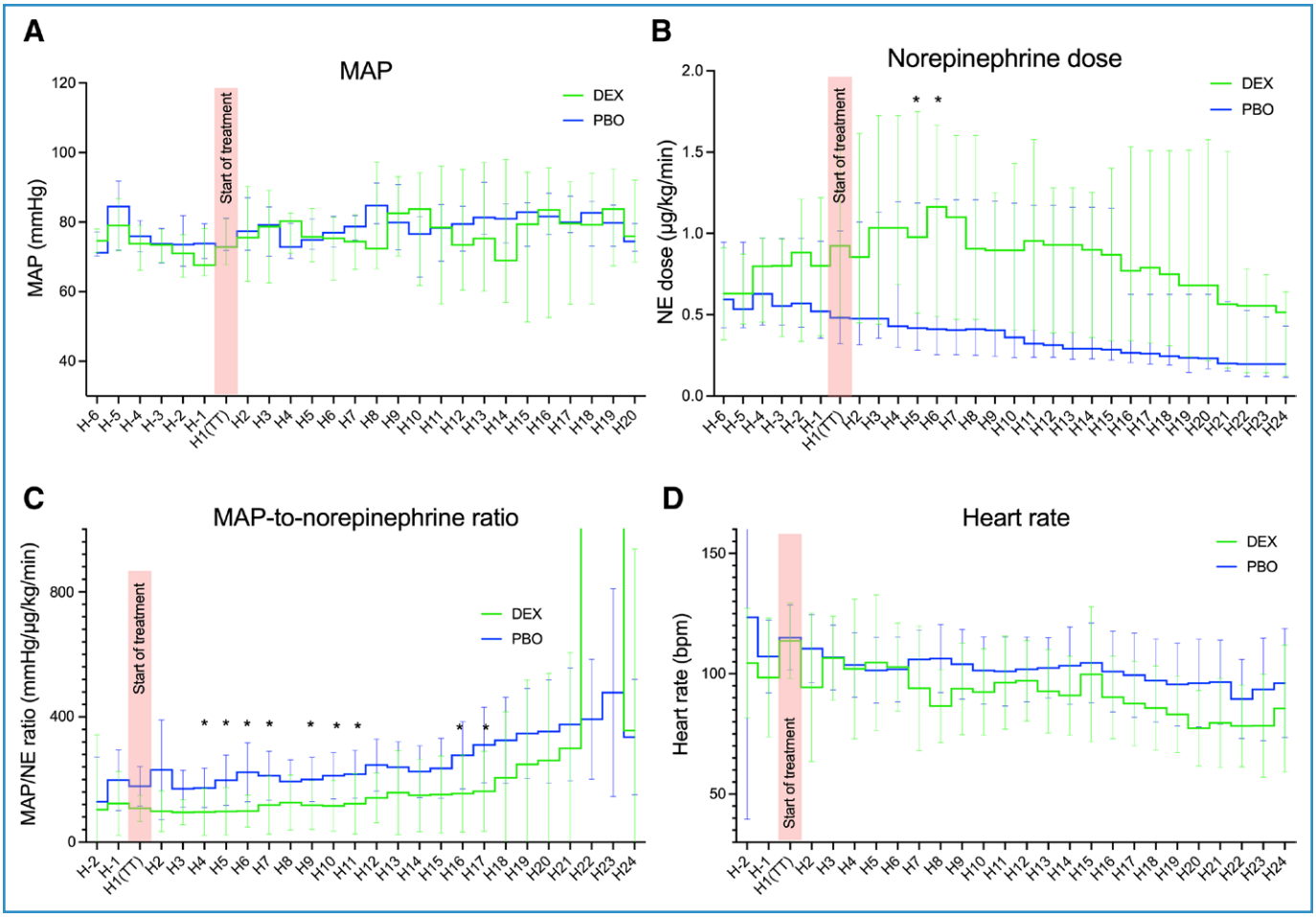

Figure 3. Evolution of circulatory parameters and norepinephrine (NE) dose in the first 24 hr. **A**, Mean arterial pressure (MAP) evolution. **B**, NE dose evolution. NE dosage is expressed in NE base equivalent. **C**, Evolution of the ratio of MAP to NE dose. **D**, Heart rate evolution. *$p < 0.05$. bpm = beats/min, DEX = dexmedetomidine, PBO = placebo.

receiving dexmedetomidine for 6 hours, but it was also the case at baseline. Patients receiving dexmedetomidine also had fewer vasopressor-free days, a higher peak dose of norepinephrine, and higher early mortality.

Baseline Characteristics Imbalance

Baseline characteristics were imbalanced between groups despite randomization, especially regarding vasopressor sensitivity, the primary outcome variable. Indeed, patients in the dexmedetomidine arm had a lower sensitivity to phenylephrine before dexmedetomidine infusion, with a significant 17% absolute difference. This imbalance between groups could be explained by sample fluctuations due to the small sample size, although it was appropriate for a pilot design. In retrospect, minimization for norepinephrine dose at randomization may have been used to circumvent this issue. The small sample size precluded adjustment for baseline differences in a multivariate regression model. This is why we performed simple sensitivity analyses whose results were consistent with the primary outcome evaluation.

Vasopressor Reactivity

The baseline difference in vasopressor resistance made the interpretation of 6 and 12 hours very difficult regarding the effect of the study treatment. Indeed, vasopressor resistance is strongly associated with early mortality (4). Thus, the higher early mortality in the dexmedetomidine arm is consistent with the higher vasopressor resistance found at baseline. However, the lack of improvement of vasopressor response between 0, 6, and 12 hours in the dexmedetomidine arm does not support dexmedetomidine efficacy, although it cannot be ruled out. Indeed, a lack

TABLE 2.
Primary and Secondary Outcomes in the Intention-to-Treat Population

Variables	Dexmedetomidine ($n = 16$)		Placebo ($n = 16$)		p
	Values	Mean ± SD	Values	Mean ± SD	
6-hr phenylephrine MAP response	14	1.26 ± 0.23	16	1.45 ± 0.26	0.048
12-hr phenylephrine MAP response	11	1.28 ± 0.23	16	1.50 ± 0.26	0.031
Cumulated norepinephrine at 6 hr or death (µg/kg)	14	983 ± 352	14	811 ± 349	0.20
Cumulated norepinephrine at 12 hr or death (µg/kg)	12	1,398 ± 522	14	1,021 ± 467	0.066
Peak norepinephrine at 6 hr or death (µg/kg/min)	15	1.84 ± 1.07	16	0.96 ± 0.59	0.011
Peak norepinephrine at 12 hr or death (µg/kg/min)	15	2.05 ± 1.32	16	0.98 ± 0.61	0.009
6-hr lactatemia (mmol/L)	15	10.14 ± 8.31	14	6.91 ± 4.41	0.21
12-hr lactatemia (mmol/L)	11	8.79 ± 9.22	14	6.09 ± 5.18	0.40
6-hr mottling score	14	1.00 ± 1.52	16	1.44 ± 1.46	0.43
12-hr mottling score	12	1.00 ± 1.54	15	1.20 ± 1.52	0.74
6-hr cardiac index (L/min/m^2)	13	3.91 ± 2.20	14	3.17 ± 1.60	0.33
12-hr cardiac index (L/min/m^2)	9	3.83 ± 1.58	13	3.09 ± 1.39	0.27
Sequential Organ Failure Assessment score					
Day 0	16	13.5 ± 2.19	16	11.75 ± 2.89	0.064
Day 1	12	11.5 ± 2.39	16	11.88 ± 3.63	0.74
Day 2	9	10.56 ± 3.68	14	10.86 ± 3.9	0.85
Day 3	9	10.22 ± 3.6	14	9.21 ± 4.44	0.56
Cumulative sedation doses (day 0–day 3)					
Midazolam (mg)	8	1,102 ± 624	8	582 ± 384	0.068
Propofol (mg)	8	14,159 ± 6,164	10	9,714 ± 4,424	0.11
Sufentanyl (µg)	11	1,418 ± 814	14	988 ± 515	0.15
		Median (Q1–Q3)		Median (Q1–Q3)	
Ventilator-free days (day 28)	16	0.00 (0.00–17.36)	16	10.03 (0.16–22.10)	0.208
Vasopressors-free days (day 28)	16	1.07 (0.00–18.39)	16	20.41 (9.25–23.36)	0.034
		n (%)		*n* (%)	
Bradycardia during treatment	16	1 (6)[a]	16	0	0.48
Death at day 3	16	8 (50)	16	2 (13)	0.022
Death during ICU stay	16	10 (63)	16	6 (38)	0.16
Death at day 30	16	11 (69)	15[b]	6 (40)	0.11
Death at day 90	16	11 (69)	15[b]	9 (60)	0.61

MAP = mean arterial pressure.

[a]The reported episode of bradycardia occurred 2 d after randomization in the context of multiple organ failure with severe hyperkalemia, acidosis, and renal failure. Another episode was reported in the Case Report Form but was not sufficiently documented, and no intervention was necessary.

[b]One patient lost of follow-up at day 26.

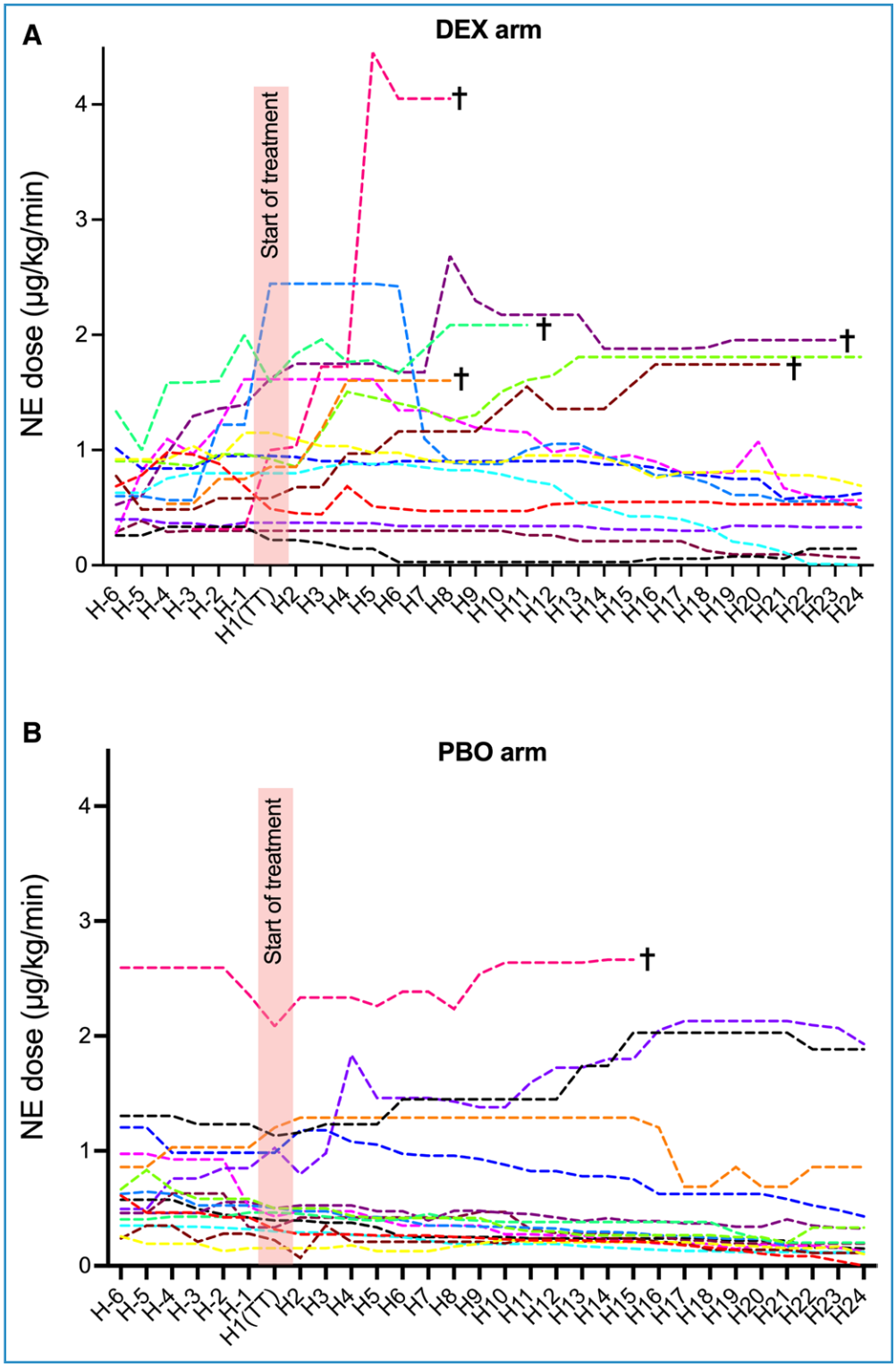
A
DEX arm
NE dose (µg/kg/min)
Start of treatment
B
PBO arm
NE dose (µg/kg/min)
Start of treatment
H-6 H-5 H-4 H-3 H-2 H-1 H1(TT) H2 H3 H4 H5 H6 H7 H8 H9 H10 H11 H12 H13 H14 H15 H16 H17 H18 H19 H20 H21 H22 H23 H24

Figure 4. Evolution of norepinephrine (NE) dose in individual patients in each arm. **A**, Individual data in the dexmedetomidine (DEX) arm. **B**, Individual data in the placebo (PBO) arm. †Patient died during the monitoring period. NE dosage is expressed in NE base equivalent.

of statistical power due to early interruption may explain this negative result. Of note, four patients with high norepinephrine doses (≥ 1 µg/kg/min) at the time of dexmedetomidine initiation showed favorable response with a rapid decrease in norepinephrine doses (Fig. 4).

Safety

Although evidence for efficacy is missing yet, we did not observe a decreased vasopressor response either with dexmedetomidine (Fig. 2). The higher mortality in the dexmedetomidine arm at the three time points (although not significant after day 3) may question further the safety of dexmedetomidine in this population. In patients with early death, norepinephrine dose trajectory was already steeply increasing when treatment was introduced (Fig. 4), with little to no change after the initiation of the study treatment.

Continuous data recorded in the first 24 hours did not raise concerns about the safety of dexmedetomidine. In particular, the HR remained unchanged between the dexmedetomidine and placebo arms, despite the relatively high dosage of dexmedetomidine. Furthermore, there was no significant difference in episodes of bradycardia between the groups. Overall, and despite the lack of evidence for efficacy, these observations do not raise concern regarding the safety of use of dexmedetomidine in this population.

Strengths and Limitations

This pilot study was designed to answer our research question with several strengths. First, it was randomized, placebo-controlled, and double-blinded; second, we used electronic recording of extensive cardiovascular monitoring for 24 hours, allowing exhaustive and unbiased data analysis for safety and efficacy; and third, as vasopressor resistance and mortality are strongly correlated, we used a validated vasopressor challenge as a surrogate for efficacy.

Our study was also limited by several issues. First, estimation of effect size was impossible due to the imbalance of baseline vasopressor resistance. Second, due to the blinding of the study treatment, dexmedetomidine was added to the current sedation of patients, and other sedative doses were not decreased during the study treatment (despite protocolized sedation). The addition of a new sedative in heavily sedated patients could have a negative effect, masking the potential benefit of dexmedetomidine itself. Third, septic shock patients' population is especially heterogeneous due to its various causes and underlying conditions. This heterogeneity may mask beneficial effects present in subgroups of patients, especially in the context of a small sample size as in this pilot trial. Finally, enrollment was slow because of the difficulty in recruiting patients with RSS. Prospective enrollment of patients with refractory shock is challenging. Indeed, patients are unstable and impose a high workload on the ICU team. Also, their condition often deteriorates very quickly between the time of inclusion, randomization, and treatment administration. Ideally, the risk of refractory shock should be anticipated to propose a therapeutic intervention before shock becomes irreversible. The threshold used in this study is lower than the most widely accepted definition of RSS (38). However, it was combined with lactate and clinical criteria, and we believe that it allowed the recruitment of patients at great risk of RSS who had an ascending norepinephrine dose (1.52 ± 1.15 µg/kg/min at randomization and 1.59 ± 1.11 µg/kg/min immediately before treatment initiation), and a 64% mortality rate. This mortality is high, but we believe it is probably a good compromise between severity and reversal potential.

Future Directions for Research

The final goal of this pilot trial was to prepare a large randomized controlled trial. This study failed to properly assess the effect-size of the intervention, which was meant to adapt the sample size calculation. However, this pilot study allowed the refinement of inclusion criteria for refractory shock patients eligible for an intervention (i.e., lower threshold combined with persistent shock signs to anticipate aggravation), to obtain data on vasopressor reactivity over time, and to evaluate early and 90 days mortality in this specific population. The design of future randomized controlled trials will benefit from these findings. Indeed, further trials are needed to determine whether the use of dexmedetomidine in RSS patients can help decrease vasopressor resistance and mortality, and which patients will benefit the most of this drug.

CONCLUSIONS

In this pilot randomized controlled trial, patients in the dexmedetomidine arm had a significantly lower response to phenylephrine at all study times (baseline, 6, and 12 hr). The imbalance of baseline characteristics might have contributed to higher early mortality in the dexmedetomidine arm and preclude to conclude on dexmedetomidine efficacy in RSS.

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Dr. Dargent conceived, designed the study, interpreted data, and drafted the article. Drs. Bourredjem and Fournel analyzed data, drafted, and revised the article. Drs. Jacquier, Bohe, Argaud, and Badie participated to data acquisition and revised the article. Dr. Levy participated to data interpretation and revised the article. Dr. Cransac participated to study conception and revised the article. Dr. Quintin conceived the study and revised the article. Dr. Quenot participated to conception and design of the study, interpretation of data, and revised the article. All authors read and approved the final article.

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The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Central Ethics Committee (Ethics Committee Sud-Est VI, Clermont-Ferrand, France, May 2019, European Union Drug Regulating Authorities Clinical Trials n°2019-000726-22, ClinicalTrials.gov NCT03953677) and by the National Drug Agency (Agence Nationale du Médicament [ANSM]) in April 2019.

All patients and/or their next/of kin gave informed and signed consent. When the patient was unable to give consent before inclusion, consent was signed by a proxy person and the informed consent of the patient was systematically sought whenever it was possible.

The datasets used during the current study are available from the corresponding author on reasonable request.

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